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ε-Amino acids based on bicyclic skeleton: bicyclo[3.3.0]octane-5-amino-1-carboxylic acids

Sung Jin Yeo,[a,✠] Kyung Seok Jeong,[a] Hogyu Han,[a] Jaheon Kim[b] and Nakcheol Jeong[a,*]

[a]*Department of Chemistry, Korea University, Seoul 136-701, Republic of Korea*
[b]*Department of Chemistry and CAMDRC, Soongsil University, Seoul 156-743, Republic of Korea*

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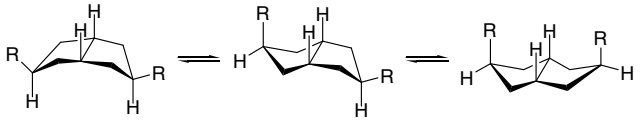
Abstract—Tsc-protected ε-amino acids, bicyclo[3.3.0]octane-5-amino-1-carboxylic acids (**1**), ready to use in the solid-phase synthesis, are prepared from 4,4-diethylcarboxylic bicyclo[3.3.0]oct-2-enone (**3**), which is available in bulk from **2** through the catalytic Pauson-Khand reaction.

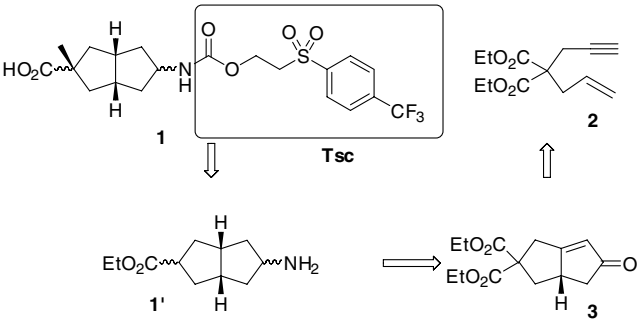
Unnatural α-amino acids[1] and their homologous amino acids have been the intensive research interests in recent years because of their utilities as surrogates for natural amino acids. β-Amino acids are a notable class in that their oligomers have been the subject of folding studies.[2] Much less is known of γ- and δ-amino acids, but the studies on this class of compounds are growing substantially.[3,4] ε-Amino acids are seldom used in this line.[5] A recent report revealed the synthesis of triazole-incorporated ε-amino acids and its application for the preparation of a cyclic hexapeptide.[6]

The skeleton of bicyclo[3.3.0]octane is interesting because it has a rigid ring junction as well as conformationally flexible side ends. One of the notable applications of this bicyclic system in peptide chemistry was bisguanidinium-bicyclo[3.3.0]octane.[7] It was used to induce the α-helix secondary structure from the oligopeptide bearing properly positioned aspartic amino acids. We are interested in ε-amino acid based on bicyclo-[3.3.0]octane because it can serve as a novel controller of the secondary structure of oligopeptides. Depending on substituents, it will select one of the possible conformers in a given circumstance (Scheme 1).



Scheme 1. The possible conformers of bicyclo[3.3.0]octane.

Meantime, we have been involved in the development of Pauson-Khand reaction. We realized that the bicyclic compound **3**, which is produced from the most-commonly used bench-marking substrate **2** for the test of the newly developed conditions, can be modified easily to give the desired ε-amino acids (Scheme 2). This approach will be practical since the catalytic Pauson-Khand reaction is well optimized to afford the compound **3** in more than 100 g at a batch.[8] Herein, we present the preparation of all possible stereoisomers of the



Scheme 2. Retrosynthetic analysis of **1**.

Keywords: Unnatural amino acid; ε-Amino acid; Bicyclic amino acid; Pauson-Khand reaction; Solid phase synthesis; Tsc amine-protecting group.
* Corresponding author. Tel.: +82 2 3290 3136; fax: +82 2 3290 3121; e-mail: njeong@korea.ac.kr
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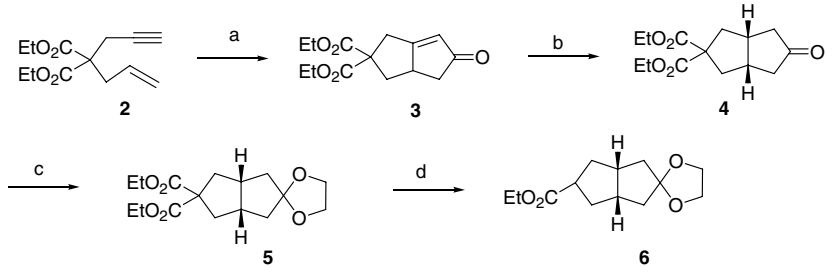
ε-amino acids **1** bearing Tsc (2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl) amine-protecting group and their use in the solid-phase peptide synthesis.

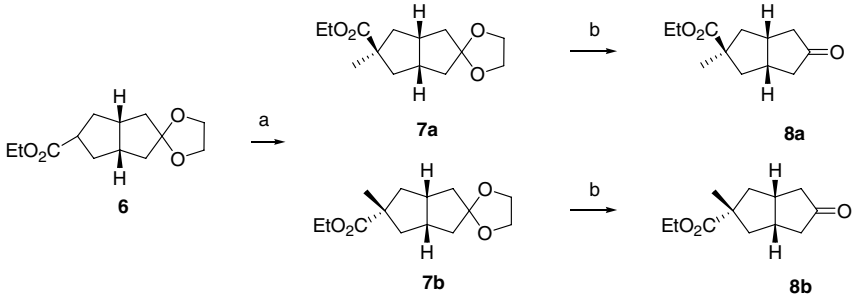
Tsc recently introduced by us is a nice substitute for Fmoc as amine-protecting group because it is compatible with Fmoc chemistry, but exhibits higher thermal and chemical stability.[9] In addition, Tsc could be installed on amine groups via base- and acid-resistant Ttc (2-(4-trifluoromethylphenylthio)ethoxycarbonyl) group, thereby allowing more options for ester hydrolysis of troublesome quaternary esters.

The precursors for ε-amino acids were prepared according to Scheme 3. The catalytic Pauson-Khand reaction of enyne **2** provided bicyclopentenone **3** in 60% on a 100 g scale. Upon hydrogenation of **3** over Pd/C in ethanol, **4** was obtained in almost quantitative yield. After protection of ketone in **4** as ketal in **5**, monodecarboxylation of **4** was successfully achieved providing compound **6** in 74% over two steps.

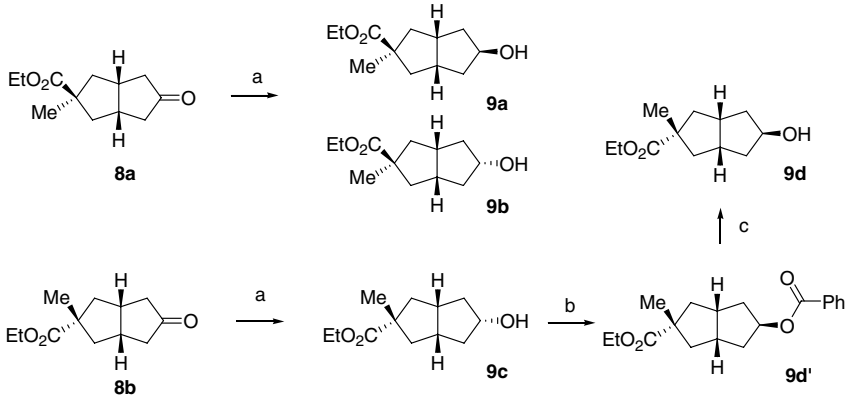
At this point, methyl group was introduced at α-position to the ester to prevent potential complication by epimerization in due course (Scheme 4). A mixture of **7a** and **7b** was obtained by treating **6** with LDA at −78 °C followed by quenching with iodomethane and then was subjected to column chromatography giving **7a** and **7b** in 17% and 77% yields, respectively. Since we wanted to have all four isomers, we did not try to optimize the selectivity to favor one over the other at this moment. Instead, each isomer was subjected to aqueous



Scheme 3. Reagents and conditions: (a) $Co_2(CO)_7[P(OPh)_3]$ (3 mol %), CO (1 atm), DME, 120 °C, 60% (100 g scale); (b) H_2, Pd/C, EtOH, rt, 95%; (c) TMSOTf, 1,2-bis(trimethylsiloxy)ethane, CH_2Cl_2, −78 °C and then rt, 97%; (d) NaCl, H_2O, DMSO, 200 °C, 76%.



Scheme 4. Reagents and conditions: (a) LDA, MeI, THF, −78 °C, (**7a**, 17%; **7b**, 77%); (b) pyridinium *p*-toluene sulfonate, H_2O/acetone, reflux, (**8a** from **7a**, 89%; **8b** from **7b**, 99%).



Scheme 5. Reagents and conditions: (a) $NaBH_4$, MeOH, rt, (**9a** from **8a**, 27%; **9b** from **8a**, 57%; **9c** from **8b**, 93%); (b) DEAD, PPh_3, benzoic acid, THF, 0 °C, 74%; (c) NaOH, H_2O/EtOH, rt, 76%.